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Editorial Comment

The Development of Thrombolytic Therapy*

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The historical note in this issue of the Journal (1) on the contribution of Agress to the subject of coronary thrombolysis is an interesting footnote in the development of thrombolytic therapy. However, the author has magnified the significance of the observation to the formative phase of this new form of therapy.

The two seminal observations that opened up a new field of investigation in the development of thrombolytic therapy were 1) the demonstration in 1949 that extravascular clots in humans could be dissolved readily by the local instillation of streptokinase (2), and 2) the demonstration in 1952 that clot dissolution could be extended to experimentally induced thrombi in rabbit ear veins by the intravenous infusion of streptokinase (3). Once the lysis of an intravascular thrombus could be achieved by the systemic administration of a thrombolytic agent, the race was on to achieve an acceptable therapy for the dissolution of human thrombi.†

The developmental work, which was now attracting other investigators as well as spurring evaluation of several potential thrombolytic agents, required experimental models in which clot lysis could be readily observed and in which appropriate hematologic studies could be carried out. Consequently, in the 1952 to 1954 period, several reports appeared describing observations made in experimentally induced thrombotic occlusions in the peripheral arteries and veins of animals using streptokinase (6), chymotrypsin (6), trypsin (6–9) and a "human plasmin" preparation (10); the latter was a streptokinase-plasminogen mixture that in contrast to streptokinase, proved to be a very powerful activator of *all* animal plasminogens (6).

Trypsin, the subject of the Agress experiment, soon was discarded as a viable thrombolytic agent. At low levels of activity, it converted prothrombin to thrombin and caused clotting; at high levels of activity, it degraded a wide variety of plasma proteins. Furthermore, preformed thrombi were not lysed when trypsin was infused intravenously (6,8,9); dissolution only occurred when the thrombus was formed in the presence of trypsin (8).

In the Agress experiment, the embolized fibrin clots were *not* dissolved by the trypsin infusions. Rather, the difference between the control and treated animals was the presence of new thrombi surrounding the fibrin emboli in the coronary vessels of the control animals and their absence in the trypsin-treated animals. Thus, the presumed formation and subsequent disappearance of thrombi in the trypsin-treated animals occurred after the start of the trypsin infusions. Consequently, the experiment did not establish that a preformed coronary thrombus could be lysed.

The experimental model created by Agress did represent a novel attempt to employ an *animal* prototype for the study of coronary thrombolysis at a time when open chest surgery would have been associated with a very high mortality. However, the randomness of the embolization with its ensuing multiple small infarcts did not emulate the clinical situation in which complete occlusion of a major artery is present with an associated transmural infarct. For this reason, and because of the deficiencies in quantitating infarct size, the model never represented a significant advance in experimental design.

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†At that time, acute coronary thrombosis (a term used synonymously with acute myocardial infarction) accounted for the largest number of admissions to an adult medical ward and was associated with an in-hospital mortality rate of approximately 30%. Therefore the primary goal for systemic thrombolytic therapy was to apply it to the treatment of acute coronary thrombosis. The delay in initiating such a study by my group (4,5) was related only to the need to wait until a highly purified preparation of streptokinase with relatively few side effects was made available by Lederle Laboratories.

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